

Functional neuroimaging using F-18 FDG PET/CT in amnesic mild cognitive impairment: A preliminary study

Madhavi Tripathi, Manjari Tripathi¹, Rajnish Sharma², Abhinav Jaimini², Maria MD'Souza², Sanjiv Saw², Anupam Mondal², Suman Kushwaha³

Departments of Nuclear Medicine and Positron emission Tomography, ¹Neurology, All India Institute of Medical Sciences, New Delhi, ²Division of Clinical PET Institute of Nuclear Medicine and Allied Sciences, ³Department of Neurology, Institute of Human Behaviour and Allied Sciences, Delhi, India

ABSTRACT

Background and Objective: People with amnesic mild cognitive impairment (aMCI) are at a higher risk of developing Alzheimers Dementia (AD) than their cognitively normal peers. Decreased glucose metabolism with F-18 fluorodeoxyglucose (FDG) positron emission tomography (PET) is a downstream marker of neuronal injury and neurodegeneration. The risk of developing AD is higher in patients with aMCI who have a pattern of AD related glucose metabolic changes on FDG-PET than those who do not have these changes. We evaluated the utility of visual and 'statistical parametric mapping (SPM)-supported reading' of the FDG-PET scans of patients clinically classified as aMCI for identification of predementia patterns and for prediction of their progression to AD (PTAD).

Patients and Methods: A total of 35 patients diagnosed as aMCI (mini mental state examination (MMSE) score ≥ 25) at the cognitive disorders and memory (CDM) clinic of speciality neurology centers were referred for a resting FDG-PET study. All patients had a detailed neurological, neuropsychological, and magnetic resonance imaging (MRI) evaluation prior to referral. Mean age of patients was 67.9 ± 8.7 (standard deviation (SD)) years, male: female (M: F) = 26:9. Twenty healthy age-matched controls were included in the study for SPM (<http://www.fil.ion.ucl.ac.uk/spm/>). Scans were interpreted visually and using SPM. Each scan was classified as high, intermediate, or low likelihood for PTAD.

Results: On visual analysis, four scans were classified as high likelihood of PTAD and revealed hypometabolism in AD related territories. Seven patients had hypometabolism in at least one AD related territory and were classified as intermediate likelihood for PTAD. Two patients had hypometabolism in other than AD territories, while 22 patients did not show any significant hypometabolism on their FDG-PET scans and were classified as low likelihood for PTAD. SPM analysis of these cases confirmed the areas hypometabolism in all 13 patients compared to a normal subgroup ($P < 0.05$). On follow-up of 24 months, all four cases with high likelihood scans had progression of cognitive deficits and were confirmed as AD in the CDM clinic while none of the others showed cognitive decline.

Interpretation and Conclusion: A pattern of AD hypometabolism on the FDG-PET study is useful for predicting PTAD. A longer follow-up of patients with hypometabolism in single AD territories is needed to predict their clinical behavior.

Keywords: Alzheimers dementia, amnesic mild cognitive impairment, fluorodeoxyglucose-positron emission tomography, positron emission tomography/computed tomography

INTRODUCTION

Mild cognitive impairment (MCI) is characterized by a decline in cognitive performance that is more pronounced than expected

for age, but is not severe enough to meet the criteria for dementia or interfere with activities of daily living.^[1] Amnesic MCI (aMCI) with cognitive deficit in the memory domain represents a putative preclinical state of Alzheimers dementia (AD). Subjects with MCI are of particular interest since they represent a population at particularly high risk for converting to AD and in which secondary prevention trials can be carried out. F-18 Fluorodeoxyglucose (FDG) positron emission tomography (PET) imaging has been proposed as a suitable modality to support the early clinical diagnosis and differential diagnosis of dementia.^[2] Most F-18 FDG-PET studies of MCI have focused on aMCI, where identification of a pattern of hypometabolism similar to that

Access this article online

Quick Response Code:



Website:
www.ijnm.in

DOI:
10.4103/0972-3919.119538

Address for correspondence:

Dr. Madhavi Tripathi, Department of Nuclear Medicine and PET, All India Institute of Medical Sciences, New Delhi - 110 029, India.
E-mail: madhu_deven@yahoo.com

of AD suggests risk for progression to AD (PTAD).^[3-5] Functional imaging with FDG-PET can serve as an objective marker to identify aMCI patients at high risk for PTAD. We undertook this study to identify patterns of metabolic abnormality on F-18 FDG-PET in patients with aMCI.

PATIENTS AND METHODS

Subjects

This was a prospective study, from December 2009 to March 2012, thirty-five patients diagnosed as MCI (using modified Petersen criteria^[1]) at the cognitive disorders and memory (CDM) clinic of speciality neurology centers were enrolled for the FDG-PET study after a detailed neurological evaluation by a dementia specialist. Vit B12 and serum thyroid stimulating hormone (TSH) levels were done in each case along with a neuropsychological evaluation. Each patient also had routine magnetic resonance imaging (MRI) examination to rule out reversible causes of cognitive dysfunction prior to referral.

A control group of 20 age, gender, and education matched subjects, with no history of any neurological or psychiatric illness were included for a normal database.

Informed consent was taken from each subject included and the need for a follow-up visit to the clinic at the end of 24 months was explained to each patient included in the study. Ethical permission was obtained from the Institutional Review Board.

FDG-PET procedure

All subjects were asked to come with at least 4 h fasting but with liberal water intake on the day of the PET study. Blood glucose level was estimated in each case and a limit of 150 mg/dl was taken for inclusion. Each patient was injected 245-296 MBq (5-8 mCi) of F-18 FDG intravenously followed by a rest period of 60 minutes with eyes open in a silent, dimly lit room followed by acquisition on a Discovery STE16 camera (General Electric Medical Systems, Milwaukee, WI, USA). This scanner has a transaxial resolution full width half maximum (FWHM) of 5.12 mm for 3-dimensional (3D) mode at 1 cm offset from the center of field of view. Patient was imaged supine with head positioned in a head rest. An initial scout of the head was followed by low dose computed tomography (CT) (120 kVp, 110 mA) of the head. Patient was moved into the PET gantry and a 3D emission scan was obtained for 20 min single-bed position. Images were reconstructed using 3D VUE algorithm and viewed on a Xeleris workstation (GE). Maximum intensity projection (MIP), plain PET and fused PET/CT images were viewed for visual interpretation which was followed by single case 'statistical parametric mapping' (SPM) analysis.

'Visual' reading

FDG-PET images were displayed scaled to a common maximum in standard color scale. During visual reading, all images from each subject were scaled to his/her own global maximal voxel value. Uniformity of reading was achieved by focusing on the

relative intensity between various cortical and subcortical regions rather than absolute values of any particular region. Each image was interpreted by an expert PET physician blinded to the clinical information.

SPM analysis

SPM-5 (<http://www.fil.ion.ucl.ac.uk/spm/>) implemented on a MATLAB platform was used for voxel based statistical analysis of images. Dicom images of patient and control groups were converted to analyze format using MRICro medical image viewer software (<http://www.psychology.nottingham.ac.uk>). The images were spatially normalized and smoothed by an isotropic 10 mm full width half maximum filter. SPM analysis was done to characterize individual patient scans using the general linear model. Each patient was compared statistically to the reference group of 20 healthy control subjects with a two-sample *t*-test. The measurements were assumed to be independent and have unequal variance between levels. Proportional scaling to the global mean was used to minimize intersubject variability. Proportional scaling basically scales each image according to a reference count, which is the global brain activity to a physiologically realistic value of 50 ml/dl/min. Hence, single-case SPM analysis essentially compares regional differences in relative glucose metabolism. At the end the SPM.mat file containing the specified design matrix was generated. Using this file contrasts were defined thus providing a map of voxels showing increased or decreased glucose metabolism in each patient as compared to the control group above the statistical threshold of $P < 0.05$. The statistical *t* maps thus obtained were overlaid onto the T1-weighted MRI template image provided by SPM5 and saved as a portable document format (PDF) for further viewing. Increased glucose metabolism was represented in 'hot' colors and decreased glucose metabolism in 'winter' colors.

Interpretation

FDG-PET scans were classified into three categories, those patients showing hypometabolism in unilateral or bilateral parietal, temporal, posterior cingulate, and precuneus on visual as well as SPM analysis will be classified as high likelihood for PTAD. Those with hypometabolism in any isolated region pertaining to the Alzheimers territory will be classified as intermediate likelihood for PTAD and those with hypometabolism not in the AD territory or corresponding to infarcts on CT or with no definite evidence of hypometabolism will be classified into low likelihood for PTAD.

Follow-up PET study

A follow-up study was obtained in eight patients who completed a 24 month follow-up. The procedure was similar to that followed in the baseline study.

Final diagnosis

The final diagnosis of dementia type was based on longitudinal clinical follow-up of at least 24 months at the CDM clinic, after the preliminary evaluation by a specialist neurologist. Clinical diagnosis was based on diagnostic systems reported in literature. Possible or probable AD was diagnosed using the National

Institute of Neurological and Communicative diseases and stroke/Alzheimers disease and related disorders association (NINCDS/ADRDA) criteria.^[6] National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) criteria were used for vascular dementia (VD).^[7]

Statistical analysis

For the purpose of comparison between visual and SPM analysis, the brain was empirically divided into 14 regions (bilateral frontal, parietal, temporal, occipital, posterior cingulate, precuneus, and cerebellar hemispheres). Subcortical grey matter regions were not considered for this regional analysis. Visual and SPM scoring was then done for each region. Agreement between visual and SPM scoring was achieved using Kappa analysis for a total of 490 regions (35 patients with 14 regions each) and on an individual patient basis. Kappa > 0.8 indicated almost perfect agreement and > 0.6 substantial agreement.

RESULTS

Demographic features of patient and control group is presented in Table 1. Mean age of the MCI patients was 67.9 ± 8.7 (standard deviation (SD)) years, male: female (M: F) ratio was 26:9. Mini mental state examination (MMSE) score was ≥ 24 in all cases. Age ($P = 0.85$) and education ($P = 0.43$) between patients and controls did not reach statistical significance.

Diagnostic classification of single patient scans on FDG-PET

A total of 35 patients underwent baseline FDG-PET study. Abnormal metabolic patterns were identified in 37% (13/35) patients [Table 2].

Four scans were classified as high likelihood for PTAD. They had hypometabolism in unilateral parietal, mesial temporal, precuneus, and posterior cingulate cortices [Figures 1a-c]. Further SPM analysis confirmed significant hypometabolism ($P \leq 0.05$) in these cortical regions [Figures 2a-c]. All four showed further cognitive deterioration and were diagnosed as AD by the specialist neurologist at the end of 24 months follow-up at the CDM clinic. Three of these cases underwent a repeat study at the end of 24 months. All

three had metabolic evidence of disease progression [Figure 3a-c] which was well-visualized on the SPM analysis also [Figure 4a-c].

Seven scans were classified as intermediate risk for PTAD and hypometabolism was present in unilateral mesial temporal or parietal cortices of one side was identified in seven (20%) patients. There was no evidence of cognitive decline clinically in any of these cases and a repeat FDG-PET study in five of these cases after 24 months did not reveal any evidence of progression in metabolic deficits.

The remaining 24 scans were classified as low likelihood of PTAD on the FDG-PET study. One patient had hypometabolism in the right basal ganglia only with no evidence of structural abnormality on CT. This case did not show cognitive deterioration when evaluated at 24 months and continues as aMCI. One case had an infarct involving the right parietal cortices and right basal ganglia identified on MRI and as hypometabolism on the PET study. This case was confirmed as vascular dementia at the end of the 24 month follow-up and MRI supported the findings. None of the remaining 22 patients with MCI showed progression of cognitive decline at the 24 months clinical follow-up.

Table 1: Demographic and clinical findings in the subjects included for the study

Characteristic	NL	aMCI
Number	20	35
Age in years	65.4 ± 7.8	67.9 ± 8.7
Education in years	18 ± 6.5	18 ± 5.4
M:F	16:4	27:9
MMSE	≥ 29	≥ 24

NL: Normal subjects, aMCI: Amnesic mild cognitive impairment, M: Male, F: Female, MMSE: Mini mental state examination

Table 2: Metabolic abnormality patterns in subjects with aMCI

Pattern of hypometabolism	Number of patients
Parietal, temporal, precuneus, posterior cingulate	2 (R)+2 (L)
Mesial temporal	2 (R)+3 (L)
Parietal	1 (R)+1 (L)
Subcortical	1
Others (infarct)	1

R: Right, L: Left, aMCI: Amnesic mild cognitive impairment

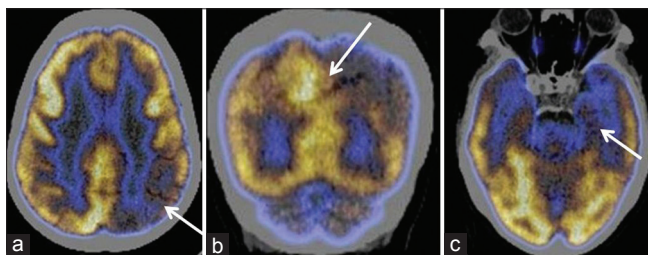


Figure 1: (a) Transaxial fused F-18 fluorodeoxyglucose positron emission tomography/computed tomography images in a case of mild cognitive impairment with mini mental state examination of 25 showing hypometabolism in the left parietal cortices (arrow). (b) Coronal fused FDG-PET/CT image showing hypometabolism in the left precuneus (arrow) and in the left parietal cortex. (c) Transaxial fused FDG-PET/CT images showing hypometabolism in the left mesial temporal cortices

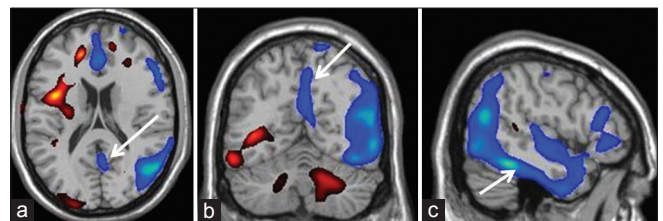


Figure 2: (a) Statistical parametric mapping t map of this case superimposed on a transaxial T1 MRI template image showing hypometabolism (blue colour) in left parietal and posterior cingulate cortices (arrow). (b) SPM t maps superimposed on coronal magnetic resonance imaging T1 template showing hypometabolism in left parietal cortex and precuneus (arrow). (c) SPM t maps superimposed on sagittal MRI T1 template showing hypometabolism in left temporal (arrow) and parietal cortices

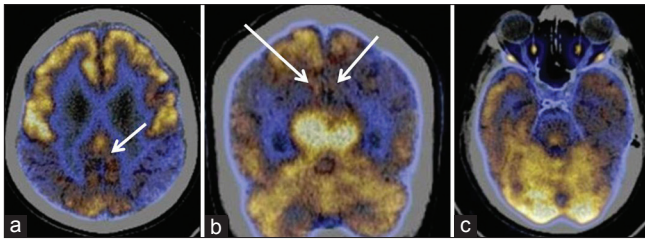


Figure 3: (a) Transaxial fused FDG-PET/CT images of the same case of MCI progressed to AD with MMSE of 20 now showing hypometabolism in the both parietal and posterior cingulate cortices (arrow). (b) Coronal fused FDG-PET/CT image showing hypometabolism in both precuneus L > R (arrow) and parietal cortices. (c) Transaxial fused FDG-PET/CT images showing hypometabolism in the both temporal (R > L) cortices

A total of 490 regions were considered for comparison of visual and SPM analysis. Kappa value for agreement between visual and SPM analysis was 0.75 indicating substantial agreement. Kappa for agreement between visual and SPM analysis on a patient-wise basis was 0.85 indicating moderate agreement.

DISCUSSION

Cerebral glucose metabolism can be evaluated using FDG-PET and this can serve as a proxy for neuronal activity at a resting state. Cerebral glucose hypometabolism on FDG-PET is a downstream marker of neuronal injury and neurodegeneration. Bilateral temporoparietal hypometabolism which includes hippocampal, posterior cingulate, and precuneal cortices; has been shown for many years to be a valid indicator of synaptic dysfunction that accompanies neurodegeneration in AD^[8,9] and can be used as a diagnostic marker from the earliest stages of disease.^[10,11] These changes become detectable in individual subjects as a significant deviation from controls 1-2 years before the onset of dementia and are closely related to cognitive impairment.^[12] Due to the importance of MCI in the early diagnosis of AD there is a growing interest in predicting future clinical changes of MCI subjects using brain imaging data. Generally, there are two kinds of clinical changes for MCI patients at future time points, first some subjects will convert into AD after some time (MCI converters) while others will never convert (non-converters). It is important to predict whether a certain MCI subject will convert into AD at a future time point or not. The other area of importance is to identify subjects with MCI for inclusion into clinical trials for neuroprotective therapies in AD.

We were able to identify an Alzheimers type pattern in 11% (4/35) of cases on the FDG-PET study, all four of these cases progressed to overt Alzheimers over the next 24 months. Hypometabolism in one territory involving the mesial temporal or parietal cortices was seen in 20% (7/35) cases, clinically none of these patients showed further cognitive decline and remained stable over 24 months. A follow-up FDG-PET was available in five cases and the metabolic pattern remained unilateral and did not progress. Though a 24 month period is insufficient to predict/rule out their PTAD, this would be an

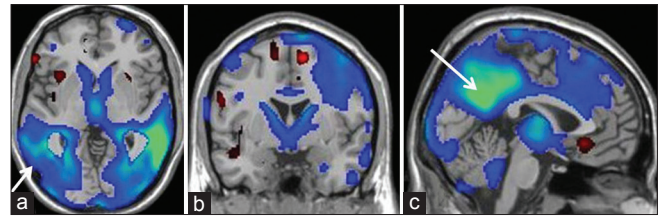


Figure 4: (a) SPM *t* maps of the same case superimposed on a transaxial MRI T1 template showing hypometabolism in both parietal cortices now R > L (R arrow). (b) SPM *t* maps superimposed on coronal MRI T1 template showing hypometabolism in both parietal and left temporal cortices. (c) SPM *t* maps superimposed on sagittal MRI T1 template showing hypometabolism in posterior cingulate and precuneus (arrow). In addition to hypometabolism in the parietal cortices, the extent of hypometabolism in the left parietal cortices has increased

interesting group to follow-up clinically and an amyloid scan in these patients would probably rule out AD earlier. Basal ganglia hypometabolism was seen in one case, likely a case of subcortical dementia. One case had hypometabolism involving parietal cortices and basal ganglia and would fall into the category of vascular dementia, where MRI would be the most useful confirmatory investigation.

We could thus successfully identify subjects with MCI at risk for PTAD using metabolic pattern on the FDG-PET study. Though those subjects with a completely normal pattern of metabolism could rule out progressive dementia (MCI non-converters) those cases showing metabolic deficits in isolated temporal or parietal cortices would need a longer follow-up to evaluate their conversion to AD. Thus, FDG-PET is extremely useful to identify patients with MCI who would likely progress to AD and serve as candidates for drug trials of early AD. FDG-PET is one of the promising new biomarkers being evaluated in the Alzheimers Disease Neuroimaging Initiative. In fact, hypometabolism on FDG-PET in MCI is being used to categorize patients into high risk and low risk for PTAD, in whom biomarkers like A β are then being compared to establish the relation with factors crucially implicated in the formation of pathological hallmarks of AD. Such studies have shown linkages between plaque pathology and glucose hypometabolism.^[13] When compared to baseline clinical testing imaging and CSF biomarkers can improve prediction of conversion from MCI to AD and FDG PET appears to add the greatest prognostic information in this regard.^[14]

Agreement between visual and SPM analysis was good indicating the utility of SPM in supporting the visual interpretation especially in centers where experienced readers are not available. SPM was particularly useful to rule out additional regions with hypometabolism when single regions showed hypometabolism on visual analysis and to identify additional regions of hypometabolism when more than two regions appeared hypometabolic visually, thus supporting Hypometabolism in Alzheimers territories.

The limitations of this study are the small sample size and the short duration of follow-up which should be at least 5 years to label them as MCI-non-converters.

CONCLUSION

FDG-PET is extremely useful to identify patients with MCI who are likely to progress to AD based on a metabolic pattern of temporoparietal, posterior cingulate, and precuneus hypometabolism.

MCI subjects with hypometabolism in a single region, temporal or parietal not associated with posterior cingulate, or precuneus hypometabolism are unlikely to progress to AD; but a longer follow-up would be required before conclusions are made and this would be an interesting subgroup for amyloid studies.

ACKNOWLEDGEMENT

This work was funded by an intramural grant from Institute of Nuclear Medicine and Allied Sciences (INMAS). We wish to acknowledge the Director INMAS (Brig RP Tripathi) for his support for the study. We also thank Dr Vijay Dhawan and Dr Shichun Peng from the Feinstein Institute for Medical Research, NSLIJHS, New York for their initial help in understanding SPM.

REFERENCES

- Petersen RC, Doody R, Kurz A, Mohs RC, Morris JC, Rabins PV, *et al.* Current concepts in mild cognitive impairment. *Arch Neurol* 2001;58:1985-92.
- Silverman DH, Gambhir SS, Huang HW, Schwimmer J, Kim S, Small GW, *et al.* Evaluating early dementia with and without assessment of regional cerebral metabolism by PET: A comparison of predicted costs and benefits. *J Nucl Med* 2002;43:253-66.
- Drzezga A, Lautenschlager N, Siebner H, Riemenschneider M, Willech F, Minoshima S, *et al.* Cerebral metabolic changes accompanying conversion of mild cognitive impairment into Alzheimer's disease: A PET follow-up study. *Eur J Nucl Med Imaging* 2003;30:1104-13.
- Mosconi L, Perani D, Sorbi S, Herholz K, Nacmias B, Holthoff V, *et al.* MCI conversion to dementia and the APOE genotype: A prediction study with FDG PET. *Neurology* 2004;63:2332-40.
- Drzezga A, Grimmer T, Riemenschneider M, Lautenschlager N, Siebner H, Alexopoulos P, *et al.* Prediction of individual outcome in MCI by means of genetic assessment and F-18 FDG PET. *J Nucl Med* 2005;46:1625-32.
- McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA work group under the auspices of Department of Health and Human services Task force on Alzheimer's disease. *Neurology* 1984;34:939-44.
- Román GC, Tatemichi TK, Erkinjuntti T, Cummings JL, Masdeu JC, García JH, *et al.* Vascular dementia: Diagnostic criteria for research studies. Report on the NINDS-AIREN International Workshop. *Neurology* 1993;43:250-60.
- Mosconi L. Brain glucose metabolism in the early and specific diagnosis of Alzheimer's Disease. FDG-PET studies in MCI and AD. *Eur J Nucl Med Mol Imaging* 2005;32:486-510.
- Anchisi D, Borroni B, Franceschi M, Kerrouche N, Kalbe E, Beuthien-Beumann B, *et al.* Heterogeneity of brain glucose metabolism in mild cognitive impairment and clinical progression to Alzheimer's disease. *Arch Neurol* 2005;62:1728-33.
- Herholz K. Cerebral glucose metabolism in preclinical and prodromal Alzheimer's Disease. *Expert Rev Neurother* 2010;10:1667-73.
- Alexander GE, Chen K, Pietrini P, Rapoport SI, Reiman EM. Longitudinal PET evaluation of cerebral metabolic decline in dementia: A potential outcome measure in Alzheimer's disease treatment studies. *Am J Psychiatry* 2002;159:738-45.
- Schmand B, Eikelenboom P, van Gool WA. Alzheimer's Disease Neuroimaging Initiative. Value of diagnostic tests to predict conversion to Alzheimer's disease in young and old patients with amnesic mild cognitive impairment. *J Alzheimer's Dis* 2012;29:641-8.
- Alexopoulos P, Guo LH, Jiang M, Bujo H, Grimmer T, Forster S, *et al.* Amyloid cascade and tau pathology cerebrospinal fluid markers in mild cognitive impairment with regards to Alzheimer's disease cerebral metabolic signature. *J Alzheimer's Dis* 2013;36:401-8.
- Prestia A, Caroli A, van der Flier WM, Ossenkoppele R, Van Berckel B, Barkhof F, *et al.* Prediction of dementia in MCI patients based on core diagnostic markers for Alzheimer's disease. *Neurology* 2013;80:1048-56.

How to cite this article: Tripathi M, Tripathi M, Sharma R, Jaimini A, MD'Souza M, Saw S, *et al.* Functional neuroimaging using F-18 FDG PET/CT in amnesic mild cognitive impairment: A preliminary study. *Indian J Nucl Med* 2013;28:129-33.

Source of Support: This work was funded by an intramural grant from Institute of Nuclear Medicine and Allied Sciences (INMAS). **Conflict of Interest:** None declared.